Transcriptional Dependencies in Diffuse Intrinsic Pontine Glioma.

Journal: Cancer Cell

Publication Year: 2017

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PubMed link: 28434841

Funding Grants: Stem Cell Mechanisms Governing Discrete Waves of Gliogenesis in the Childhood Brain, White matter neuroregeneration after chemotherapy: stem cell therapy for “chemobrain”

Public Summary:
This paper seeks to identify a more effective therapeutic strategy for a deadly childhood cancer called diffuse intrinsic pontine glioma (DIPG). DIPG is thought to arise from neural precursor cells in the childhood brain and malignancy is thought to be due to dysregulation of gene expression. Here we tested different ways to disrupt gene expression in the cancer cells and found that disruption of gene transcription is a very effective therapeutic strategy. We also took a close look at the genes that are primed for expression in DIPG and found evidence to support the concept that these pediatric brain tumors arise from neural precursor cells that contribute to developing the brain's white matter (oligodendrocyte precursor cells).

Scientific Abstract:
Diffuse intrinsic pontine glioma (DIPG) is a fatal pediatric cancer with limited therapeutic options. The majority of cases of DIPG exhibit a mutation in histone-3 (H3K27M) that results in oncogenic transcriptional aberrancies. We show here that DIPG is vulnerable to transcriptional disruption using bromodomain inhibition or CDK7 blockade. Targeting oncogenic transcription through either of these methods synergizes with HDAC inhibition, and DIPG cells resistant to HDAC inhibitor therapy retain sensitivity to CDK7 blockade. Identification of super-enhancers in DIPG provides insights toward the cell of origin, highlighting oligodendroglial lineage genes, and reveals unexpected mechanisms mediating tumor viability and invasion, including potassium channel function and EPH receptor signaling. The findings presented demonstrate transcriptional vulnerabilities and elucidate previously unknown mechanisms of DIPG pathobiology.